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ORIGINAL ARTICLE

Prognostic value of systemic immune-inflammatory index in hospitalized adolescent COVID-19 patients

Hastanede yatan adölesan COVID-19 hastalarında sistemik immün-inflamatuvar indeksin prognostik değeri

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ABSTRACT

Background: A new parameter called systemic immune-inflammatory index (SII), which is based on neutrophil-lymphocyte ratio (NLR) and platelet count, is used to examine the inflammatory and immune status of patients. The aim of this study was to evaluate the prognostic value of SII in adolescents diagnosed with COVID-19 and to compare SII with other biomarkers including C-reactive protein (CRP)/albumin (Alb) ratio, D-dimer, lactate and NLR.
Methods: The medical records of hospitalized adolescent COVID-19 patients between April 1, 2020, and March 31, 2022, were retrospectively reviewed. A cutoff value for SII was obtained to examine the predictive value of SII for intensive care unit (ICU) admission as the primary outcome.
Results: A total of 177 patients with a mean age of 165.89 ± 26.60 months were included in the study. 97 (54.8%) of the patients were male. The most common presenting symptom was fever (n = 102, 57.6%). Median (IQR) SII was 799 (951), lactate 1.9 (1.53), NLR 10.19 ± 6.77 and CRP/Alb ratio 1.55 (2.61). The cut-off value for SII in predicting ICU admission was ≥1111 (sensitivity, 78.6%; specificity, 75.2%; + likelihood ratio, 3.32; - likelihood ratio, 0.30; AUC: 0.768) (p < 0.001). While SII and CRP/Alb ratio were better than lactate in predicting ICU admission (p = 0.03 and p = 0.04, respectively), there was no statistical difference between SII and CRP/Alb ratio (p > 0.05).
Conclusion: The results of this study suggest that a high SII during hospitalization is associated with an increased likelihood of ICU admission in patients hospitalized with COVID-19. Although additional studies are needed to confirm and validate these findings, the evidence of this study supports that SII is a valuable prognostic predictor of hospitalized patients with COVID-19.

Keywords: Adolescent, COVID-19, prognoses, systemic immune-inflammatory index

ÖZ

Giriş: Nötrofil-lenfosit oranı (NLR) ve trombosit sayısına dayanan sistemik immün-inflamatuar indeks (SII) adı verilen yeni bir parametre, hastaların inflamatuar ve immün durumunu aynı anda değerlendirmek için kullanılmaktadır. Bu çalışmanın amacı COVID-19 tanısı alan adölesanlarda SII'nin prognostik değerini değerlendirmek ve SII'yi C-reaktif protein (CRP) / albümin (Alb) oranı, D-dimer, laktat ve NLR gibi diğer prognostik belirteçlerle karşılaştırmaktır.
Gereçler ve Yöntem: Hastanede yatan adölesan COVID-19 hastalarının 1 Nisan 2020 ve 31 Mart 2022 tarihleri arasındaki tıbbi kayıtları retrospektif olarak incelendi. Birincil sonlanım noktası olarak yoğun bakım ünitesine kabul kullanıldı. SII'nin yoğun bakım ünitesine kabul için öngörücü değeri hesaplandı ve diğer biyobelirteçler ile karşılaştırıldı.
Bulgular: Yaş ortalaması 165,89 ± 26,60 ay olan 177 hasta çalışmaya dahil edilmiştir. Hastaların 97 (54,8%) tanesi erkekti. En sık görülen başvuru semptomu ateşti (n = 102, %57,6). SII 799 (951), laktat 1.9 (1.53) mmol/L, NLR 10.19 ± 6.77 ve CRP/Alb oranı 1.55 (2.61) idi. Yoğun bakım kabulü öngörmede SII için cut-off değeri ≥1111 idi (sensitivite, 78,6%; spesivite, 75,2%; + likelihood ratio, 3,32; - likelihood ratio, 0,30; AUC: 0,768) (p < 0,001). SII ve CRP/Alb oranı yoğun bakıma kabulü öngörmede laktattan daha iyi iken (sırasıyla p = 0,03 ve p = 0,04), SII ve CRP/Alb oranı arasında istatistiksel fark yoktu (p > 0,05).
Sonuç: Bu çalışmanın sonuçları, COVID-19 ile hastaneye yatırılan adölesan hastalarda hastaneye yatış sırasında yüksek SII'nin artmış yoğun bakım kabulü ile ilişkili olduğunu göstermektedir. Bu bulguları doğrulamak ve geçerli kılmak için ek çalışmalara ihtiyaç duyulmasına rağmen, bu çalışmadan elde edilen kanıtlar, COVID-19 hastalarında hastane içi sonuçların değerli bir prognostik göstergesi olarak SII'nin potansiyel faydasını desteklemektedir.

Anahtar Kelimeler: adölesan, COVID-19, prognoz, sistemik immün-inflamatuvar indeks

Introduction

The past five years, COVID-19 caused more than 7 million deaths with approximately 750 million confirmed cases (1). In the early stages of the pandemic, COVID-19 was thought to affect mainly middle-aged and elderly people, and the incidence in children was lower. However, the incidence in children was underestimated due to low testing rate (2). Children with COVID-19 have with milder symptoms and are less likely to experience severe disease or death than adults (3,4). Obesity may worsen the prognosis of COVID-19 (5). It has also been shown that adolescents with the delta variant of COVID-19 require more oxygen support, have an increased need for endotracheal intubation, and experience prolonged hospital stays (6).

A new parameter called systemic immune-inflammatory index (SII), which is based on neutrophil-lymphocyte

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ratio (NLR) and platelet count, is used to assess the inflammatory and immune status of patients. In addition to cancer patients, SII has also been associated with poor outcomes and mortality in coronary artery disease, chronic heart failure, and intracranial hemorrhage (7-10). In a recent meta-analysis, Yuan et al. (11) highlighted the association between admission SII and the risk of in-hospital mortality in patients with COVID-19.

Age-related differences in the clinical course of COVID-19 are still under investigation; one hypothesis suggests that differences in immune system function and maturation in young children compared to adults (12). The aim of this study was to evaluate the prognostic value of SII in adolescents diagnosed with COVID-19 and to compare SII with other biomarkers including C-reactive protein (CRP)/albumin (Alb) ratio, D-dimer, lactate and NLR.

Methods

This study included patients aged 10-18 years who were diagnosed with COVID-19 and hospitalized between April 1, 2020 and March 31, 2022. The diagnostic criteria for COVID-19 were accepted a positive polymerase chain reaction (PCR) test and/or chest computed tomography (CT) findings indicative of viral pneumonia. Patients with missing data, patients aged >18 years or <10 years, those with hematologic or solid organ malignancy, those receiving immunosuppressive treatment for any reason, and those with any chronic disease were excluded from the study. The World Health Organization defined individuals between the ages of 10-19 as adolescents. We excluded patients aged 19 because admission to pediatric clinics is legally limited to 18 years old in Turkey (13). The local ethics committee approved the study (decision number 2024/5037).

Patient demographics, admission symptoms, laboratory results (CBC, C-reactive protein, D-dimer, lactate, albumin), SII score calculated as (neutrophil-to-lymphocyte ratio) x platelet count, CT findings (pleural effusion, ground-glass opacities, consolidation), hospital stay duration, intensive care unit (ICU) admission, and mortality were recorded.

Data analyses

Normality of the distribution was assessed using the Kolmogorov-Smirnov test. Continuous data were presented as mean ± standard deviation for variables with a normal distribution and as median and interquartile range (IQR) for variables with a non-normal distribution. Categorical data were presented as frequencies and percentages. The primary outcome was ICU admission. The effect of various factors on ICU admission was evaluated using chi-squared or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for numerical variables. We analyzed the performance characteristics of CRP/Alb ratio, lactate, and SII levels in predicting ICU admission using receiver operating characteristic (ROC) curves. We determined cut-off values using Youden's index and compared them with DeLong's method. MedCalc statistical software (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org), version 20.110 was used for all analyses. A p-value of <0.05 was considered statistically significant.

Results

During the study period, 265 patients were hospitalized with a diagnosis of COVID-19 infection. Twelve patients were excluded due to hematologic malignancy, 2 patients due to solid organ malignancy, 5 patients due to immunosuppressive treatment, 27 patients due to asthma, 11 patients due to cerebral palsy, 8 patients due to diabetes mellitus, 7 patients due to epilepsy, 6 patients due to chronic renal failure, 4 patients due to congenital heart disease, 1 patient due to cystic fibrosis, and 5 patients due to missing data. Finally, 177 patients with a mean age of 165.89 ± 26.60 months were included in the study. Ninety-seven (54.8%) patients were male and 80 (45.2%) were female. The most common presenting symptom was fever (n = 102, 57.6%), followed by cough (n = 98, 55.4%) and weakness (n = 56, 31.6%). One hundred and fifty-eight (89.3%) patients had positive CT findings. The median (IQR) SII was 799 (951), lactate was 1.9 (1.53), and the CRP/Alb ratio was 1.55 (2.61). The mean ± SD NLR was 10.19 ± 6.77. Fourteen (7.9%) patients required ICU admission and 1 (0.6%) patient died. The demographic, clinical, and laboratory findings of the patients are summarized in Table 1.

There were significant differences in CRP (p = 0.021), albumin (p = 0.016), CRP/Alb ratio (p = 0.003), lactate (p = 0.043), and SII (p = 0.001) between patients in the inpatient ward and those in the ICU, while no significant differences were observed in age, sex, WBC, lymphocyte count, neutrophil count, NLR, and D-dimer (p > 0.05). The comparison between inpatient ward and ICU patients is summarized in Table 2.

Table 1. Demographic, clinical and laboratory findings of the study population

Number of patients	177
Age, months, mean ± SD	165.89 ± 26.60
Gender, n (%) Male Female	 97 (54.8) 80 (45.2)
Symptoms, n (%) Cough Fever Weakness Dyspnea Muscle pain Throat ache Diarrhea Anosmia Headache Vomiting Rhinorrhea Ageusia Rash	 98 (55.4) 102 (57.6) 56 (31.6) 37 (20.9) 48 (27.1) 49 (27.7) 21 (11.9) 29 (16.4) 22 (12.4) 16 (9) 18 (10.2) 17 (9.6) 5 (2.8)
Computed tomography findings, n (%) Negative Positive Pleural effusion Ground-glass opacity Consolidation	 19 (10.7) 158 (89.3) 25 (15.8) 129 (81.6) 65 (41.1)
White blood cell, 10^9/L, mean ± SD	12.68 ± 5.90
Neutrophil, 10^9/L, mean ± SD	10.55 ± 5.47
Lymphocyte, 10^9/L, mean ± SD	1.33 ± 0.73
Neutrophil/lymphocyte ratio, mean ± SD	10.19 ± 6.77
C reactive protein, mg/L, median (IQR)	89.8 (104.36)
Albumin, g/L, mean ± SD	36.91 ± 7.2
C reactive protein/Albumin ratio, median (IQR)	1.55 (2.61)
Lactate, mmol/L, median (IQR)	1.9 (1.53)
D-dimer, µg/mL mmol/L, median (IQR)	5.5 (8)
Systemic immune-inflammatory index, median (IQR)	799 (951)
Length of stay in hospital, days, median (IQR)	4 (3)
Intensive care unit admission, n (%)	14 (7.9)
Endotracheal intubation requirement, n (%)	3 (1.69)
Mortality, n (%)	1 (0.6)
IQR: interquartile range, n: number, SD: Standard Deviation	

Table 2. Comparison of inpatient ward and ICU patients

	Inpatient Ward (n=163, 92.1%)	ICU (n=14, 7.9%)	*p* value
Age, months, mean ± SD	165.07 ± 27.12	175.5 ± 17.59	0.058
Male gender, n (%)	92 (56.4)	5 (35.7)	0.166
White blood cell, 10^9/L, mean ± SD	12.65 ± 6.03	12.97 ± 4.28	0.846
Neutrophil, 10^9/L, mean ± SD	10.54 ± 5.55	10.69 ± 4.58	0.909
Lymphocyte, 10^9/L, mean ± SD	1.31 ± 0.71	1.44 ± 0.94	0.534
Neutrophil/lymphocyte ratio, mean ± SD	10.03 ± 6.51	12.04 ± 9.35	0.287
C reactive protein, mg/L, median (IQR)	71.86 (96.91)	140.1 (190.1)	**0.021**
Albumin, g/L, mean ± SD	37.29 ± 7.11	32.51 ± 6.7	**0.016**
C reactive protein/Albumin ratio, median (IQR)	1.46 (2.63)	4.38 (5.17)	**0.003**
Lactate, mmol/L, median (IQR)	1.9 (1.23)	3.1 (5.47)	**0.043**
D-dimer, µg/mL mmol/L, median (IQR)	5.2 (8)	9.8 (8)	0.232
Systemic immune-inflammatory index, median (IQR)	772 (884)	1728 (1797)	**0.001**
ICU:intensive care unit, IQR: interquartile range, n: number, SD: Standard Deviation			

The performance characteristics of SII, lactate, and the CRP/Alb ratio for predicting ICU admission were calculated (Table 3). The cutoff value for ICU admission was a SII of >1111 ($p < 0.001$). While a SII and CRP/Alb ratio were better than lactate in predicting ICU admission ($p = 0.03$ and $p = 0.04$, respectively), there was no statistical difference between SII and CRP/Alb ratio ($p > 0.05$) (Figure 1).

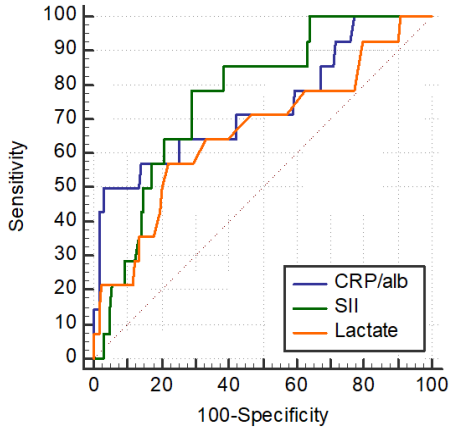

Figure 1. The ROC curves of SII, CRP/Alb ratio and lactate

Discussion

The COVID-19 pandemic was a global health issue that affected communities worldwide. Both therapeutic and predictive diagnostic management of COVID-19 are necessary to combat this problem. In this retrospective study, we evaluated the predictive value of SII determining the ICU admission in hospitalized adolescent patients with COVID-19. In cases when the SII calculated at the time of emergency department admission is >1111, there is an increased likelihood of ICU admission [+LR 3.32 (95% CI 2.4-4.5)]. While the SII was a better predictor than lactate, the predictive value was similar with CRP/Alb ratio. The findings of our study indicate that SII can serve as an indicator of inflammatory processes associated with the development of critical illness or ICU admission in patients hospitalized with COVID-19.

The SII comprises three peripheral blood parameters that provide a comprehensive summary of the immune and inflammatory status of patients. As ecpected, it has been previously identified as a prognostic biomarker in sepsis patients (14). In a recent study, Fois et al. (15) reported that patients with higher SII values exhibited significantly worse PaO□/FiO□ ratios and chest CT severity scores among those diagnosed with COVID-19. It was suggested that SII may serve as

Table 3. Comparison of ROC curves of SII, lactate and CRP/Alb ratio

	Sensitivity % (95% CI)	Specificity % (95% CI)	+LR % (95% CI)	-LR % (95% CI)	AUC % (95% CI)	*p* Value
SII (>1111)	78.6 (49.2-95.3)	75.2 (68.6-83.1)	3.32 (2.4-4.5)	0.30 (0.11-0.8)	0.768 (0.70-0.83)	<0.001
Lactate (>2.8mmol/L)	57.1 (28.9-82.3)	77.9 (70.8-84.0)	2.59 (1.5-4.4)	0.55 (0.30-1.0)	0.663 (0.59-0.73)	<0.05
CRP/Alb raito (>3.92)	69.7 (44.7-91.3)	95.3 (90.9-98.9)	3.31 (2.3-4.7)	0.52 (0.31-0.9)	0.738 (0.67-0.80)	<0.001

AUC: Area under the curve, CI: Confidence interval, LR: Likelihood ratio, SII: Systemic immune-inflammatory index, CRP/Alb: C-reactive protein/albumin

a marker of lung damage in patients with COVID-19 rather than a reflection of their overall clinical condition (16). While SII has been established as a prognostic marker in adults for various critical illnesses, our study is the first to investigate to delineate SII as a prognostic factor in adolescent patients.

Several mechanisms may explain the observed association between a high SII and an increased risk of ICU admission and worse prognosis in patients hospitalized for COVID-19. A high SII may reflect an increased inflammatory (elevated neutrophils) and thrombotic (elevated platelets) status along with worsening immune dysfunction (decreased lymphocytes). A study from China demonstrated that a high SII can effectively predict severe COVID-19 cases as defined by the National Guidelines for the Diagnosis and Treatment of COVID-19 (17). Furthermore, patients with a high admission SII were more likely to require ICU admission due to the severity of their disease (18). Finally, an elevated admission SII has been identified as a predictor of adverse in-hospital events in patients with COVID-19, including invasive mechanical ventilation, acute limb ischemia, and acute venous thrombotic events. These complications may collectively contribute to an increased risk of worsen prognosis (19-21).

The CRP/Alb ratio has been established as a prognostic biomarker in patients with septic shock, pancreatitis, and acute mesenteric ischemia (22). In a recent study, Yılmaz et al. (23) demonstrated that the CRP/Alb ratio is a valuable biomarker for predicting mortality in pregnant patients. Lactate is the primary end product of anaerobic metabolism. In the absence of oxygen, tissues typically exhibit increased lactate production, as pyruvate cannot be oxidized in the Krebs cycle due to oxygen deprivation and is instead converted to lactate. A systematic review of the literature revealed that patients with worse outcomes due to COVID-19 often exhibited higher blood lactate values than those with better outcomes at the early stages of the disease (24). In this study, both the CRP/Alb ratio and lactate were found to be associated with ICU admission, with results consistent with those reported in the literature.

The NLR is a reliable, readily available, and inexpensive biomarker that has been used as a prognostic indicator in numerous studies, including those examining sepsis, cardiovascular disease, and malignancy (25,26). NLR has been demonstrated to be a robust predictor of prognosis in patients diagnosed with COVID-19 (27,28). However, in this study, the NLR, which is a component of the SII, was unexpectedly not associated with ICU admission. This discrepancy may be attributable to our patient number, the relatively small sample size in our study compared to others, as well as the severity of SARS-CoV-2 infection, which was not evaluated in this study (25-28).

The major limitations of our study were that its single-center design, retrospective nature and unequal sample sizes between inpatient ward and ICU. Additionally, we were unable to evaluate the laboratory parameters after treatment. Other factors that may affect laboratory indices such as obesity, admission day, could not be assessed due to missing data. Prospective cohort studies are needed to confirm the reliability of SII.

The results of this study suggest that a high SII during hospitalization is associated with an increased likelihood of ICU admission in patients hospitalized with COVID-19. Although additional studies are needed to confirm and validate these findings, the evidence from this study supports the potential utility of SII as a valuable prognostic indicator for ICU admission outcomes in patients with COVID-19. Incorporating SII assessment into clinical practice may help identify patients at higher risk of adverse outcomes and facilitate more targeted and timely interventions to improve patient care and management.

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Conflict of interest statement

The authors have no commercial associations or sources of support that might pose a conflict of interest.

Author contribution statement

All authors have made substantial contributions to

all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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